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## An unusual clinical and biochemical presentation of ornithine transcarbamylase deficiency in a male patient

A. B. Burlina · A. Peduto · A. Di Palma · A. Bellizzi ·  
D. Sperli · A. Morrone · A. P. Burlina

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**Summary** We report a male patient with a history of recurrent idiopathic vomiting, normal plasma ammonia and glutamine concentrations in acute phase, who died at 3 years of age. Ornithine transcarbamylase deficiency was diagnosed after detecting elevated urinary orotate concentrations in a sample collected just before death, and the diagnosis was confirmed by DNA analysis.

Late-onset ornithine transcarbamylase (OTC; EC 2.1.3.3) deficiency (McKusick 311250) is one of the most difficult urea cycle defects to recognize owing to the variety of its clinical and biochemical signs (Brusilow and Horwich 2001).

In this report, we describe an Italian child, B.N., a second twin, born at term from unrelated healthy parents. Among the mother's relatives, three siblings (one female and two

male) are in good health. He was breast-fed for 6 months, then breast feeding was stopped. He was poorly receptive to formula feeding thereafter and suffered from recurrent vomiting. Weight and height were normal during the first year of life. At 15 months of age, he was referred to a tertiary hospital after a day of persistent vomiting and somnolence alternating with periods of irritability. Weight was at 75th centile (12 kg). According to his parents, the child had no aversion to proteins (daily intake 2.5 g/kg) and the episodes seemed to be more related to fructose ingestion. Mild hepatomegaly was present and the electroencephalogram showed bilateral slow activity. Routine biochemical investigations showed elevated transaminases (AST 300 U/L, ALT 1727 U/L) but normal ammonia (40  $\mu$ mol/L; normal values 35–75), lactate, plasma amino acids (Table 1) and acylcarnitine profile by tandem MS. Serology for hepatitis viruses A, B and C was negative. The clinical signs disappeared spontaneously after glucose infusion over the next 24 h.

To confirm suspected fructosaemia, the patient was evaluated in our Unit. Physical examination revealed normal growth (weight and height at 50th centile); however, the weight had increased only slowly in the previous 3 months; the liver was palpable one finger-breadth below the right costal margin. The laboratory findings on the morning of admission showed normal ammonia, plasma amino acids and urinary organic acids (orotate 1.2 mmol/mol creatinine, normal values <2.5; and uracil 54 mmol/mol creatinine, normal values <64.5). Serum transferrin (Tf) analysis by capillary zone electrophoresis showed an increased trisialo-Tf form, suggesting a possible diagnosis of fructosaemia. The patient was put on a low-fructose diet and molecular analysis for aldolase B gene mutation was performed.

About 4 months later, he was readmitted to the local hospital with severe acute encephalopathy after a day of continuous vomiting. Brain CT scan showed severe oedema.

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A. B. Burlina (✉) · A. Peduto  
Metabolic Unit, Department of Pediatrics, Azienda Ospedale –  
Università di Padova, Via Giustiniani 3, 35128 Padua, Italy  
e-mail: burlina@pediatria.unipd.it

A. Di Palma · A. Bellizzi  
Division of Pediatrics, General Hospital, Trento

D. Sperli  
Cosenza

A. Morrone  
Metabolic Unit, Department of Pediatrics, University Hospital,  
Florence

A. P. Burlina  
Department of Neuroscience, Neurological Clinic, University  
Hospital, Padua, Italy

**Table 1** Plasma amino acid profiles in stable clinical conditions and during encephalopathic crisis

Amino acid	Normal status ( $\mu\text{mol/L}$ )	Acute crisis <sup>a</sup> ( $\mu\text{mol/L}$ )	Normal values <sup>b</sup> ( $\mu\text{mol/L}$ )
Phenylalanine	88	230	26–91
Tyrosine	74	98	24–115
Methionine	29	52	4–47
Leucine	154	202	49–216
Isoleucine	66	94	22–107
Histidine	101	117	41–125
Valine	284	319	74–321
Threonine	102	97	35–226
Arginine	99	106	10–140
Lysine	125	157	48–284
Ornithine	66	45	10–163
Proline	185	243	59–369
Glutamate	100	169	5–150
Glutamine	721	621	254–823
$\gamma$ -Aminobutyrate	22	26	4–31
Glycine	202	217	127–341
Taurine	95	117	10–170
Serine	151	197	69–187
Alanine	369	456	152–547
Aspartate	10	63	1–24
Asparagine	55	47	23–112
Citrulline	15	22	8–46

<sup>a</sup>Sample collected just before death<sup>b</sup>Modified from Shih VE (2003) In: Blau N, Duran M, Blaskovics ME, Gibson KM, eds. *Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases*. New York: Springer

Liver transaminases were increased (AST 557 U/L, ALT 1923 U/L); ammonia, which was monitored closely, was initially normal and only reached a value of 120  $\mu\text{mol/L}$  at the end stage; plasma amino acids (Table 1) were normal. Despite treatment with hyperosmolar agents, the child died the following morning. Urinary organic acids collected before his death showed peaks of orotic acid and uracil (270 and 685 mmol/mol creatinine, respectively), suggesting an OTC deficiency. OTC gene analysis disclosed a missense mutation in exon 3, containing an adenine-to-thymine transversion (base 264), changing codon 88 from lysine to asparagine. The mother and second twin were found to carry no such mutation.

## Discussion

This observation emphasizes the great heterogeneity of clinical and biochemical signs of OTC deficiency, which can pose considerable diagnostic difficulties not only in the detection of carriers but also in late-onset presentations in males (Steiner and Cederbaum 2001).

In this patient, ammonia and amino acid assays, which play a pivotal part in the diagnosis of OTC deficiency, were performed either during the acute phase (the day after the glucose infusion) or during the metabolic assessment a month after the acute episode, when we decided that an allopurinol challenge test was unnecessary given that all the metabolic

parameters, including urinary orotic acid, were normal. The urinary organic acid analysis performed in the last sample collected before the child's death unexpectedly showed an increase in orotic acid and orotidine concentrations, as well as in uracil. Surprisingly, the plasma sample collected at the same time showed only mildly raised ammonia and no plasma amino acid abnormalities.

It has been reported that plasma ammonia concentrations can be normal in OTC patients as a consequence of the protein intake (Spada et al 1994). Oddly, plasma glutamine was also normal, even in the acute stage. We can offer no clear explanation for such an unusual finding at present. Similar biochemical findings had already been reported in an 8-year-old Italian boy with recurrent episodes of bizarre behaviour and an unremarkable metabolic work-up (Spada et al 1994). A diagnosis of OTC was ultimately reached after a one-day high-protein diet and subsequent orotic acid assay in the patient's urine.

Despite his normal plasma glutamine levels, our patient developed a severe cerebral oedema. It is well known that brain oedema is a characteristic and often terminal symptom in urea cycle disorders. The brain oedema in OTC deficiency may be due to the swelling of astrocytes, in which glutamine may have a role (Bachmann 2002), a cytotoxic oedema with cell swelling, and a reduction in extracellular space.

As for the molecular analysis, our findings are as intriguing as the biochemical features. The patient had a mutation in codon 88, exon 3, resulting in the substitution of

asparagine for lysine two codons upstream from the putative carbamyl phosphate binding site coding domain. This rare mutation has been reported in patients with a mild, late-onset presentation (Reish et al 1993). Furthermore, it has been suggested that such a mutation does not completely abolish OTC activity (McCulloch et al 2000). To our knowledge, ours is the first reported case of a male patient with OTC deficiency presenting such a complex and dramatic clinical picture, with plasma ammonia and glutamine levels remaining constantly normal even during acute metabolic decompensation.

In conclusion, the diagnosis of OTC deficiency has to be considered when a child has recurrent idiopathic vomiting with neurological signs despite normal ammonia and plasma glutamine in the acute phase.

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